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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/463,890	04/28/2000	ULRICH H. KOSZINOWSKI	203676	6925

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EXAMINER
SAJJADI, FEREYDOUN GHOTB

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/463,890	KOSZINOWSKI ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,37 and 40-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,37 and 40-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response dated April 28, 2009, to the non-final action dated December 30, 2008, has been entered. No claims have been amended, cancelled or newly added. Accordingly, claims 36, 37 and 40-70 remain pending in the application and are under current examination.

Response & Maintained Claim Rejections - 35 USC § 103

Claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. (of record), in view of Chartier et al. (J. Virol. 70:4805-4810; 1996). The rejection set forth on pp. 3-4 of the previous Office action dated December 30, 2008 is maintained for reasons of record.

The rejection has been reiterated as follows:

Messerle et al describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions (i.e., due to complementation between the two vectors upon co-transformation in eukaryotic host cells). The ability of the BAC vectors to produce infectious virus evidences that each of the vectors comprise "parts of the genome of a virus that are indispensable for replication and packaging". Furthermore, Messerle et al. describe production of the BAC vectors by cotransfection in *E. coli* cells. Messerle et al. state that the purpose of constructing the BAC vectors was to facilitate the exchange of nonessential viral genes by any gene of choice without the need for further selection. Moreover, Messerle et al. notes that human CMV as well as mouse CMV comprises a region that is probably not essential for replication *in vitro* and clearly views human CMV as a potential vector.

While Messerle et al. describe their BAC vectors as comprising two fragments, the generation of large full-length viral vectors by homologous recombination in *E. coli* was known in the prior art.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract). Such is depicted in Figure 1, p. 4806, showing *in vivo* homologous recombination between sequences that include the ITRs (i.e. identical to each other) and the generation of virus plaques after transfection by calcium phosphate (first column, p. 4807) in human (293) or mammalian cells to produce pure Ad5 virus (first column, p. 4810). Thus providing the motivation to apply the methodology to generate full-length infectious virus.

The teachings of Messerle et al. and Chartier et al. are both directed to the reconstitution and generation of infectious viral vectors. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to combine their respective teachings and to use homologous recombination mediated by *E. coli*, to generate infectious HSV in a host cell, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to generate a sequence contiguous HSV BAC vector, because such would obviate the need to manipulate two separate BAC fragments.

Claims 43 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Ehtisham et al. (1993) J. Virol. 67:5247-5252. The rejection set forth on pp. 4-5 of the previous Office action dated December 30, 2008 is maintained for reasons of record.

The rejection has been reiterated as follows:

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While Messerle et al. and Chartier et al. do not describe their viruses as including gamma herpes virus MHV68, such was known in the prior art. The method of Chartier et al. is further applicable to any large virus genome.

Ehtisham et al. describe murine herpes virus 68 (MHV-68) as a naturally occurring murine herpes virus closely related to the EBV of primates. (See especially the first paragraph after the abstract).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, to apply homologous recombination mediated by *E. coli*, to generate infectious MHV-68 in a host cell, as instantly claimed, with a reasonable expectation of success, at the time of the instant invention. A person of ordinary skill in the art would have been motivated to generate a sequence contiguous MHV-68 BAC vector, because such would obviate the need to manipulate two or more separate BAC fragments.

Claims 45-50 and 52-56 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Gage et al. (1992) J. Virol. 66:5509-5515. The rejection set forth on pp. 5-6 of the previous Office action dated December 30, 2008 is maintained for reasons of record.

The rejection has been reiterated as follows:

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While Chartier et al. describe recombination between the ITRs of the virus, neither Messerle et al. nor Chartier et al. describe recombination involving loxP sites. However, such was known in the prior art.

Gage et al. describe a method of inserting plasmid DNA into a herpes virus genome by Cre-lox recombination wherein the bacterial sequences are flanked by loxP sites (see especially the paragraph bridging pages 5509-5510, Figure 1 and the caption thereto) and further state the method has many advantages over methods of inserting bacterial DNA by homologous recombination using marker transfer (see especially the first full paragraph on page 5514).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to modify the method of producing a BAC comprising an infectious herpes virus genomic sequence according to the method of Gage et al. such that the product BAC comprises bacterial nucleic acid sequences flanked by loxP sites, with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to use the method of Gage et al. in view of the many advantages of the method described in the teachings of Gage et al. because Gage et al. demonstrates the efficacy of the Cre-lox system for inserting bacterial DNA into the herpes virus genome.

Claims 60-62 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al. in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view Chen et al. (1987) Mol. Cell. Biol. 7:2745-2752. The rejection set forth on pp. 6-7 of the previous Office action dated December 30, 2008 is maintained for reasons of record.

The rejection has been reiterated as follows:

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While Chartier et al. describe calcium phosphate mediated transfected of 293 cells, neither Messerle et al. nor Chartier et al. describe transfection of NIH3T3 fibroblasts. However, such was known in the prior art.

Chen et al. describe a method of efficiently transformation eukaryotic cells, including NIH3T3 cells, by a method involving calcium phosphate coprecipitation. (See especially the Abstract and Table 1)

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to transfect NIH3T3 cells, with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to use the NIH3T3 cells, because Chen et al. state that the method provides efficient transformation for introducing DNA.

Claims 67-70 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Messerle et al., in view of Chartier et al. (J. Virol. 70:4805-4810; 1996), as applied to claims 36, 37, 40-42, 45, 51, 57-60, and 63-66 above, and further in view of Luckow et al. (1993) J. Virol. 67:4566-4579 (of record). The rejection set forth on pp. 7-8 of the previous Office action dated December 30, 2008 is maintained for reasons of record.

The rejection has been reiterated as follows:

The claims are directed to a method of mutagenizing the infectious herpes virus genomic sequence of claim 36 comprising introducing the BAC of claim 36 into a bacterial host and exposing the BAC to mutagenizing DAN molecules, wherein there is a transposon in the mutagenizing DNA molecules.

Messerle et al. describe reconstituting two BAC/MCMV hybrid fragments wherein the hybrid vectors comprise BAC sequences and an infectious viral genomic sequence of >200kb (i.e. 235 kb minus ~15 kb), and further disclose that the constructs were used to produce MCMV virions. Messerle et al. state that the BACs will facilitate the exchange of nonessential viral genes by any gene of choice.

Chartier et al. describe the generation of recombinant Ad5 adenovirus vectors by homologous intermolecular recombination in *E. coli*, to generate fully infectious particles in permissive cells (Title and Abstract).

While neither Messerle et al. nor Chartier et al. describe mutagenizing the infectious HSV genomic sequence with a transposon, such was known in the prior art.

Luckow et al. describe the construction and use of BAC vectors that comprise an infectious viral genome sequence operatively fused to a mini-F replicon that allows autonomous replication and stable segregation of plasmids at low copy number in E. coli. The BAC vectors further comprise a selectable kanamycin resistance marker and attTn7 sites that allow transposon-mediated insertion of heterologous nucleic acid sequences into the vector (e.g. Abstract; page 4567, columns 1-2, bridging paragraph; Figure 1). Luckow et al further describe transposon-mediated mutagenesis at the attTn7 sites of different BAC vectors in *E. coli* to generate new vectors comprising a heterologous sequence encoding a desired polypeptide. (See especially the section entitled "Transposition of mini-Tn7 elements to target bacmids" bridging the left and right columns on page 4573).

Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art, at the time the invention was made to combine their respective teachings and use the transposon mediated DNA exchange described by Luckow et al. for the purpose of exchanging nonessential viral genes with gene of choice in the BACs of Messerle et al., with a reasonable expectation of success at the time of invention by Applicants. One would be motivated to combine the teachings of the prior art because Messerle et al. teaches that intended use of the BAC vectors described therein is to facilitate the exchange of nonessential CMV viral genes by any gene of choice and Luckow et al. teaches that the method of the transposon mediated DNA exchange described thereby provides many advantages over other methods of engineering viral genomic DNA comprised in BACs that were known in the prior art. (See especially the first full paragraph on page 4577.)

Response to Arguments:

Applicants traverse the rejection, arguing the Messerle reference does not disclose a BAC containing all genes essential for the generation of an infectious herpes virus in a host cell; that the Chartier reference discloses assembling a 36 kb adenovirus genome in E. coli, which is considerably smaller than the size of the herpes virus genome as presently claimed, and uses plasmids, not BACs, for assembling adenovirus genomes. Applicants' arguments have been fully considered, but are not found persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prior art of Messerle et al. discloses the cloning of the full length MCMV genome as bacterial artificial chromosome (BAC) in *E. coli*, wherein the plasmids were stably replicated and maintained in *E. coli*, and were subsequently cotransfected into eukaryotic cells. Thus, there is no requirement for Chartier et al. to disclose the same.

Applicants argue that the Chartier reference discloses plasmid recombination in *E. coli*, while the claimed BAC is produced by recombination in eukaryotic cells; and with reference to the Declaration under rule 1.132, by co-inventor Martin Messerle, argue that the Chartier reference is not suitable for generating virus genomes that are larger than an adenovirus genome (i.e. larger than 36 kb).

Such is not found persuasive, because there is no teaching or suggestion in Chartier et al. to limit the size of a cloned virus genome to 36 kb. While the full-length Ad5 genome of Chartier et al. is 36 Kb, the issue is whether the recombination competent *E. coli* BJ5183 recBC sbcBC strain disclosed by Chartier can recombine and generate a single BAC clone from overlapping BAC clones of Messerle et al. Thus, the statements in the 1.132 Declaration regarding the size limitations of various plasmid vectors in Chartier et al. is irrelevant. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

The rule 1.132 Declaration states that the genome of herpers viruses is complex, and contains numerous direct and indirect sequence repeats and a herpes virus genome contained in a BAC vector would not be supported by the *E. coli* recBC sbcBC strain used in the Chartier reference. Such is not found persuasive, because a person of ordinary skill in the art having co-transformed the BAC vectors of Messerle et al. into Chartier's *E. coli* BJ5183 recBC sbcBC strain, would not need to subject the recombinants to further long-term propagation in the same

stain, and would introduce the recombinants into the *E. coli* recombination deficient DH10B strain of Messerle et al. for subsequent screening in eukaryotic cells, as disclosed by both Messerle et al. and Chartier et al.

Furthermore, that the *E. coli* BJ5183 recBC sbcBC strain is capable of generating HSV recombinants by recombination is evidenced by Kong et al. (J. Virol. Methods 80:129-136; 1999), teaching an *in vivo* recombination cloning procedure that supports the routine manipulation of relatively large DNAs, such as two cosmids comprising overlapping DNA fragments of HSV-1 to generate plasmids up to 65 kb in size (Abstract and Table 4, p. 134). It should be ntoed that cosmids have a lower size capacity for clones, than the BAC vectors disclosed by Messerle et al.

Applicants' arguments with respect to changing the principle of operation of the prior art invention are mis-placed, because the person or ordinary skill in the art would not utilize the plamids of Chartier et al. for the recombination, but would simply introduce the BAC vectors of Messerle et al. into the *E. coli* BJ5183. The recombination events mediated by the *E. coli* BJ5183 strain are not plasmid specific and the person of ordinary skill in the art would be so apprised.

Thus, the rejections are maintained for reasons of record and the foregoing response.

Conclusion

Claims 36, 37 and 40-70 are not allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Primary Examiner, Art Unit 1633